31 optically pure R(-) isomer of albuterol sufficient to result in bronchodilation while simultaneously reducing undesirable side effects, said R isomer being substantially free of its S(+) isomer,

REMARKS

Claims 1-6, 8 and 15-18 were present in the application as filed under 37 CFR 1.62. Claims 15 to 18 are canceled by amendment above. Claims 1-6 and 8 are therefore pending in the application.

In the office action of February 25, claims 1-6 were rejected under 35 USC §103 as obvious over Muittari et al. (Chem. Abs. 89:12359m). As explained in the Preliminary Remarks submitted December 7, 1993, Muittari deals strictly with the effects of racemic albuterol. Applicants do not believe Muittari could suggest anything about the advantages attendant upon the use of a single enantiomer.

Claims 1-6 and 8 were also rejected over Brittain et al., Hartley et al. and Buckner et al. As explained in the interview of May 3, and in the Preliminary Remarks of December 7, each of the Brittain, Hartley and Buckner references discusses the pharmacology of the individual enantiomers, but none suggests any advantage in diminution of side effects to be gained from the use of the pure R enantiomer, which is the substance of applicants' claimed invention.

Applicants have found that when isolated guinea pig tracheal muscle preparations were subjected to graded doses of a spasmogen, the contractile response to the spasmogen was significantly increased in bronchial tissue strips that had been incubated with S-albuterol. No such effect was seen in the tissues that had been incubated with R-albuterol. They concluded that the increased sensitivity to spasmogens from treatment with S-albuterol was due to a direct effect on

bronchial smooth muscle.

Subsequent to the filing of applicants' original application, Morley et al. and Chapman et al. (references provided with the response of February 16, 1993) independently disclosed that the S isomer in bronchial tissue causes a hypersensitivity to allergen. British patent application 2,255,503, filed (by Morley and Chapman) more than a year after applicants' '262 application, makes a similar disclosure and presents claims very similar to applicants'.

After reviewing the foregoing issues in the interview of May 3, the examiner indicated that he felt there might be patentable subject matter related to avoidance of side effects that show up on chronic medication with racemic albuterol. He felt that a claim in the format of amended claim 1 above could be allowable if two issues could be resolved: (1) whether support exists in the specification for the restriction of the method to avoidance of side effects in chronic therapy and (2) whether Dr. Aberg's showing of July 23, 1993, is commensurate with the original disclosure.

The first of these concerns is addressed in the accompanying declaration under 37 CFR 1.132 of T. Scott Johnson, M.D. Dr. Johnson explains that although the term "chronic" does not appear in the specification as originally filed, the person of ordinary skill in the art would expect that albuterol would be given chronically, since that is the common mode of therapy. Moreover, the concept of chronic administration is implicit in the description of modes of administration that is found in the specification. In particular, on page 4 in the paragraph extending from line 4 to line 13, and page 5, line 6 to line 9, the prophylactic therapy described makes medical sense only if chronic administration is intended.

As to the second point, applicants' agent believes that

the seminal case on the question of the correspondence between a showing and the scope of the original disclosure that he and the examiner were seeking is *In re Zenitz* (142 USPQ 158). Zenitz was claiming compounds and applicants are claiming a method of use, so the analogy is not perfect, but the reasoning appears apposite. In *Zenitz* the applicant had disclosed that the compounds sought to be patented were useful as sedatives and hypotensive agents, but had not discussed any separation between sedation and hypotensive effects as an advantage of his compounds. In support of the unobviousness of the compounds, he provided an affidavit showing the unexpected separation of hypotensive and sedative effects in certain of these compounds. The examiner held, and the Board of Appeals affirmed, that since the separation of effects was not originally disclosed, Zenitz could not rely on that in his showing.

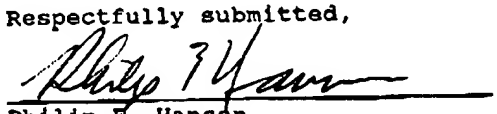
However, the CCPA reversed the decision of the Board of Appeals on the basis that the unexpected utility, although not specifically disclosed, would nevertheless flow from the disclosed utility. Applicants believe that the same reasoning applies to their situation: applicants did not specifically disclose airway hyperreactivity as a side effect to be avoided by the use of the pure R isomer; however, airway hyperreactivity is certainly a side effect and avoiding airway hyperreactivity could be said to reasonably flow from the disclosure of avoiding side effects. Thus applicants believe that the declaration of Dr. Gunnar Aberg submitted July 23, 1993, and the articles by Chapman and Morley reinforcing that declaration, provide appropriate support for the claims to "avoiding side effects" consistent with the holding of the CCPA in *Zenitz*.

The CCPA in *Zenitz* distinguished their decision from *In re Herr* (134 USPQ 176). In *Herr*, the utility disclosed for

the compounds sought to be patented was solely as chemical intermediates and the affidavit proffered by Herr alleged utility as anabolic and androgenic agents. The court found that the anabolic and androgenic utility would not flow from their disclosed utility as intermediates. Applicants believe that the situation in the present case is analogous to *Zenitz* and can be distinguished from *Herr* on the same basis as that provided by the CCPA.

In light of the foregoing amendment, declaration and explanation, it is believed that the application is in condition for allowance and such is respectfully requested.

Respectfully submitted,



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